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EXAMINER	
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ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/867,274	Paszty et al.
Examiner	**Art Unit**
Scott D. Priebe, Ph.D.	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 17, 2003*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-5, 8-36, and 38-62* is/are pending in the application.

4a) Of the above, claim(s) *8-10, 12-36, 38-51, and 55-62* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-5, 11, and 52-54* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *May 29, 2001* is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 7
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restriction

Applicant's election with traverse of Group I, claims 1-5, 11, 52-54, in Paper No. 10 filed 3/17/03 is acknowledged. The traversal is on the ground(s) that search of all the inventions would not impose serious burden on the Office, that the restriction between combination and subcombination, between a product and a method of making a product, between a product and using the product, and unrelated inventions was improper.

This is not found persuasive because first, Applicant has incorrectly characterized the restriction as being between related distinct inventions, when the restriction was based only in part between related distinct inventions and in part on unrelated, independent inventions (e.g. see pg. 6-7 of the restriction requirement). Also, evidence for a search burden has been established in the restriction requirement. For example, the separate classification of many of the inventions is evidence of a search burden, as is the divergent subject matter, e.g. protein vs. antibody vs. hybridoma vs. nucleic acid vs. transgenic animal, and the full search for each of the inventions is not required for the other inventions. For example, in order to determine the patentability of the nucleic acid, no search need be made for the protein (e.g. based on its sequence) or the antibody, etc. or for the various methods of using the nucleic acid and especially not for the various methods of using the protein and antibody, etc. (page 7).

With respect to combination-subcombination, first claim 62 has been amended and is not a multiple dependent claim. The particulars of the subcombination are not required for the transgenic animal of claim 62, which can be made with any one of the nucleic acids recited in claim 1, e.g. SEQ ID NO: 1 and 3 are not identical to each other and need not be identical to a nucleic acid encoding SEQ ID NO: 2 or 4, respectfully, or to a nucleic acid that hybridizes to any of these.

With respect to product and process of making it, a method of making the protein involving purification of the protein from tissue obtained from a mouse is materially different than the recombinant method claimed. The method does not use cultured cells, nor would the mouse tissue comprise the vector of claim 4.With respect to product and process of using it, it is respectfully suggested that Applicant read the claims and note the products implicitly or explicitly required to carry out each method. They differ, as does the goal of each method. For example, Group II requires a cultured host cell and conditions (and therefore the means for providing the conditions) for producing and isolating the protein. In contrast, group V requires a compound, hopefully one which inhibits or blocks production of the protein, and the means for detecting inhibition of production of the protein, e.g. a hybridization probe for detection of mRNA levels. The products used in each are different, as is the goal of each. With respect to the unrelated inventions, claim 12 misjoins two unrelated methods, one involving identification of a compound which inhibits expression of the protein, and the second involving identification of a compound which inhibits the activity of the protein, i.e. inhibits the protein itself. The first

requires means for detecting either nucleic acid, e.g. a probe, or protein, e.g. an antibody, while the second requires an assay for protein activity.

The requirement is still deemed proper and is therefore made FINAL.

Claims 8-10, 12-36, 38-51, 55-62 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 10.

Specification

The disclosure is objected to because of the following informalities: SEQ ID NOs: 4 and 6 do not agree with Fig. 2A-C or with SEQ ID NO: 3, which would not encode SEQ ID NO: 4 or 6. SEQ ID NO: 4 and 6 are missing three consecutive amino acids, GlyAlaArg, corresponding to amino acids 173-175 (GAR) from Fig. 2B, and amino acids 196-198 in Fig. 2C. Claims reciting SEQ ID NO: 4 were examined using the sequence disclosed in Fig. 2B, rather than SEQ ID NO: 4.

Appropriate correction is required.

Claim Rejections - 35 USC § 101

Claims 1-5, 11, 52-54 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility. In the absence of a specific and substantial asserted utility, credibility could not be assessed.

The claims are directed to nucleic acid molecules which encode a polypeptide having an activity of the polypeptide of SEQ ID NO: 2, human Cloaked-2 protein, or SEQ ID NO: 4, murine Cloaked-2 protein. The specification discloses, based only on structural features, that the Cloaked-2 protein is distantly related to proteins of the cystine-knot growth factor structural super-family. The specification provides no evidence identifying a specific function for the Cloaked-2 protein at any level. It does not disclose any biochemical function, other than the vague assertion that it would bind an unidentified receptor, presumably since other members of the super family, e.g. TGFβ, PDGF, NGF, bind receptors to initiate cellular processes. It does not disclose any physiological function for Cloaked-2 either at the level of a cell, of a tissue, or an organism. Beyond the disclosed nucleotide and predicted amino acid sequences, the specification presents information only on tissues which express Cloaked-2 mRNA, strongest in heart and kidney.

The specification asserts that the claimed nucleic acid molecules, the polypeptides encoded thereby or antibodies may be used to treat or diagnose a "nonexclusive list" of apparently unrelated diseases (pages 99-103). The assertion appears to be based on the unsubstantiated hypothesis that Cloaked-2 has hormonal or growth-factor activity, and the expression pattern seen for Cloaked-2 mRNA expression. The specification does not disclose whether the goal for such treatment should be the increase or augmentation of Cloaked-2 activity or its inhibition or decrease. The specification does not identify any activity of Cloaked-2 whose excess or loss would correspond to any of the listed diseases or conditions. Consequently, the

specification provides no basis that would lead one of skill in the art to reasonably accept that the specification disclosed a method for treatment or diagnosis of any of the diseases or conditions listed in a readily available form. Consequently, it would be left to one of skill in the art to reasonably confirm or refute these asserted uses, and to determine which, if any, the claimed nucleic acid molecules could be used for either directly as a means for diagnosis or treatment, or indirectly as a means for making or identifying a product usable for diagnosis or treatment. The disclosure of highly speculative, general and nebulous uses as here does not meet the requirement for a specific and substantial utility. *In re Kirk*, 153 USPQ 48, 52 (CCPA 1967)

In addition, Brunkow et al. (Am. J. Hum. Genet. 68: 577-589, Feb. 2001) discloses a mammalian gene called *SOST*, which in human and mouse encodes a protein identical to instant SEQ ID NO: 5 and 6, respectively, which are the precursor forms of SEQ ID NO; 2 and 4, respectively (see Fig. 6). As shown in Fig. 7 of Brunkow, SOST is expressed in bone and cartilage far more than in any other tissue. Loss of *SOST* function in humans leads to sclerosteosis, which is characterized by progressive skeletal bone growth, with normal osteoclast function and defective osteoblast function, and no endocrinological abnormalities, (i.e. its not a hormone). Brunkow et al., US 6,395,511 discloses that BEER protein (a.k.a. SOST) binds to and inhibits the function specifically of BMP-5 and BMP-6, i.e. not a growth factor, but a growth factor inhibitor (see Abstract and claim 1). There is no evidence whether or not BEER/SOST/CLOAKED-2 binds a cellular receptor as suggested in the instant specification. It is significant that none of the diseases listed in the instant specification relate to bone or cartilage

disorders or include sclerosteosis, and sclerosteosis is not characterized by any of the conditions listed in the specification. The Brunkow article was published after the date to which priority is being claimed, and the Brunkow patent issued after the instant application was filed, and most important the instant specification fails to disclose even a hint of what either Brunkow reference discloses concerning the activity and uses of the claimed nucleic acid. Consequently, this information cannot be used to supplement the deficiencies in the instant specification, since the specification must set forth the uses and the utility requirement must be met when the application is filed. *In re Kirk*, 153 USPQ 48, 52 (CCPA 1967).

The specification (pp. 81-82) suggests using the claimed nucleic acid molecules in microarray methods to identify and validate Cloaked-2 disease-related genes, which the specification fails to disclose, as therapeutic targets; and for drug discovery. However, the specification fails to provide any nexus between Cloaked-2 and any disease, pharmacological effects of Cloaked-2, Cloaked-2 inhibitors or their pharmacologic effects, clinical trials in which Cloaked-2 expression would be a marker or what a change in its expression would indicate, or what "Cloaked-2-related small drugs" would be used for. In short, there is insufficient information in the specification to envision what immediate benefit these activities would provide to the public. The specification (pp. 80-81) mentions using the claimed nucleic acid molecules to make transgenic animals having either a disrupted Cloaked-2 gene or an exogenous Cloaked-2 transgene for overexpression of Cloaked-2. However, the specification does not disclose what phenotypic result would be obtained in either type of animal, nor does it assert a

use for transgenic animals with a disruption. The specification asserts that transgenic animals which overexpress Cloaked-2 could be used to screen drug candidates for those which counteract the effects of overexpression. However, one would first have to make the animal to determine whether any physiological effect would occur. In short, the only readily apparent use for making such transgenic animals is for identifying a function for Cloaked-2.

Uses for the nucleic acid molecules to make polypeptides, or the polypeptides to make antibodies, or simply for detection of homologous nucleic acids in a sample do not meet the requirement for a specific utility, since all nucleic acids which encode proteins have these uses. The use of a product as an intermediate or starting product to produce a final product meets the utility requirement only if the final product has a specific, substantial and credible use. *Brenner v. Manson*, 148 USPQ 689, 696 (US 1966); *In re Kirk.*

At best, the disclosed uses appear aimed only at characterizing Cloaked-2 and its function to satisfy scientific curiosity or for identifying or reasonably confirming an unsubstantiated, speculative substantial use for the claimed nucleic acid molecules. Such uses fails to meet the utility requirement. The Supreme Court has held that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. "[A] patent system must be related to the world of commerce rather than to the realm of philosophy." *Brenner v. Manson*, 148 USPQ 689, 696 (US 1966). The instant specification provides no more than suggestions of avenues of further characterization of Cloaked-2 and identification of potential uses, without reasonably assuring the public of any benefit derived therefrom in an immediately available form

as required under §101. There is no evidence of record for a well established utility for an essentially uncharacterized gene or protein in general, or for Cloaked-2 specifically, at the time the claimed invention was made.

Claims 1-5, 11, 52-54 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 1-5, 11, 52-54 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with the claims, and;

claims 1-5, 11, 52-54 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a nucleic acid molecule which encodes a polypeptide having "an activity of the polypeptide as set forth in SEQ ID NO: 2 or SEQ ID NO: 4," or the complement of such a nucleic acid molecule. Claims 1 and 2 place limits on the structural similarity between the nucleic acid and SEQ ID NO: 1 or SEQ ID NO: 3 or between the

polypeptide encoded and SEQ ID NO: 2 or SEQ ID NO: 4, or limit the nucleic acid molecule to a splice variant or allelic variant of SEQ ID NO: 1 or SEQ ID NO: 3. Claim 3 is simply directed to a nucleic acid molecule encoding a polypeptide that is not identical to SEQ ID NO: 2 or 4, but has an activity of them. The specification enables how to make and provides an adequate written description for a nucleic acid molecule which encodes a polypeptide with "an activity of the polypeptide as set forth in SEQ ID NO: 2 or SEQ ID NO: 4", wherein the nucleic acid molecule either comprises SEQ ID NO: 1 or SEQ ID NO: 3 or encodes SEQ ID NO: 2 or SEQ ID NO: 4. The specification neither enables how to make nor adequately describes any other nucleic acid molecule which encodes a polypeptide with "an activity of the polypeptide as set forth in SEQ ID NO: 2 or SEQ ID NO: 4."

While the written description and enablement requirements are separate and generally separable requirements, the instant application fails to meet either requirement for essentially the same reasons. The primary reason is that the specification fails to identify a single "activity of the polypeptide as set forth in SEQ ID NO: 2 or SEQ ID NO: 4", whether biochemical, biological or physiological. Indeed, it cannot be determined from the specification whether the polypeptide of SEQ ID NO: 2 has an activity of the polypeptide of SEQ ID NO: 4, and *vice versa.* For example, the specification provides no evidence that the human Cloaked-2 would complement the loss of Cloaked-2 function in a mouse, or that the human Cloaked-2 would bind the same mouse receptor as murine Cloaked-2, if one assumes that Cloaked-2 acts by binding a cellular receptor as do other characterized members of the cystine-knot protein super family. The specification

also fails to provide a single method or assay for determining whether a given nucleic acid molecule meeting the structural limitations of the claims, e.g. hybridization, percent identity, allelic variant or splice variant, encodes a polypeptide actually having an activity of the polypeptide as set forth in SEQ ID NO: 2 or SEQ ID NO: 4. While a polypeptide of SEQ ID NO: 2 or 4 may reasonably be assumed to have an activity characteristic of itself, whatever that may be, any specific variant of these polypeptides cannot be assumed to have such an activity given the dearth of descriptive and enabling support in the specification as to what that activity is or how to determine it. For example, if one of skill in the art were provided a nucleic acid molecule encoding a polypeptide differing from SEQ ID NO: 2 by a single amino acid, the specification does not provide any descriptive support that would allow one to envision whether the polypeptide would have the requisite activity, nor does it describe a method enabling one to determine by experimentation whether the encoded polypeptide had the requisite activity, i.e. one would be unable to determine whether the nucleic acid molecule was embraced by the claims. One would be unable to determine whether the change would result in a loss of polypeptide function, an alteration of polypeptide function, e.g. a dominant-negative mutation, or would be a neutral or silent change.

With respect to allelic or splice variants, these are naturally occurring sequence variations. The specification does not provide the sequence for a single such variant, nor does it provide objective evidence that such variants even exist. In order for a splice variant to exist, the primary mRNA must at least include introns which may be differentially spliced. The

specification does not provide any genomic sequence information, and does not disclose if the corresponding genes even contain introns or if the primary mRNA is even spliced or if spliced, whether it can be differentially spliced. Brunkow et al. (2001) and Balemans et al. (Hum. Molec. Genet. 10 (5): 537-554, 2001) disclose that the *SOST* gene has two exons and one intron. Thus, it is unlikely that its mRNA can be differentially spliced. If one were provided a nucleic acid molecule differing from SEQ ID NO: 1 or 3, the specification provides no information that would allow one to determine whether the sequence arose in nature, i.e. an allelic or splice variant, or was a sequence created by man which has no counterpart in nature. With respect to allelic variants, the specification provides neither a description nor a method for determining whether the allele is a functional allele or a non-functional allele or whether a splice variant has an activity of the polypeptide of SEQ ID NO: 2 or 4.

The court and the Board have repeatedly held (*Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,*18 USPQ2d 1016 (CA FC, 1991); *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993); *Fiddes v. Baird*, 30 USPQ2d 1481 (BPAI 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)) that an adequate written description of a nucleic acid requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it, irrespective of the complexity or simplicity of the method; what is required is a description of the nucleic acid itself. It is not sufficient to define DNA solely by its principal biological property, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any DNA with that biological property. Naming a type of material

generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. When one is unable to envision the detailed constitution of a complex chemical compound having a particular function, such as a nucleic acid, so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the nucleic acid has been isolated. Thus, claiming all DNA's that achieve a result without defining what means will do so is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. Also, where a claim purports to cover all nucleic acids that encode a specific protein and the specification discloses but a single DNA known to do so, the situation is analogous to a single means claim and does not meet the enablement requirement under para. 1 of §112. The court has also held that a claimed nucleic acid could meet the written description and enablement requirements if the nucleic acid were defined by a disclosed process found, after-the-fact, to produce the nucleic acid, and claimed as a product-by-process. However, in the instant case, the nucleic acids are not claimed as a product-by-process, nor does the specification disclose any process known to yield a claimed nucleic acid other than those which yield a nucleic acid encoding SEQ ID NO: 2 or 4.

In terms of the structural requirements of the nucleic acid molecules, the only difference between the cases reviewed by the court and Board, and the instant case, is that in addition to recitation of a desired protein activity, claims 1 and 2 also recite a broad arbitrary structural relationship between the claimed nucleic acid sequence, either in terms of its nucleotide sequence

or the polypeptide encoded, and the single disclosed species of nucleotide sequence and amino acid sequence, respectively. Claim 3 is directed to any nucleotide sequence encoding a polypeptide with an activity of SEQ ID NO: 2 or 4, except for SEQ ID NO: 2 or 4. Consequently, the claims do not purport to claim *all* nucleotide sequences which encode a particular functional protein. However, this distinction does not aid Applicant's cause here. The recited structural relationships are arbitrary since neither the specification nor the prior art discloses any definitive relationship between protein function and % identity or homology at either the nucleotide or amino acid level; and the specification does not describe a single species of nucleic acid that encodes a functional protein that is not either 100% identical to SEQ ID NO: 1 or 3 or that encodes a polypeptide that is not 100% identical to SEQ ID NO: 2 or 4.

While one of skill in the art can readily envision numerable species of nucleic acid sequences that hybridize to a reference nucleotide sequence under a given set of conditions and that encode a polypeptide at least a given % identity to a recited reference amino acid sequence, one cannot envision which of these also encode a polypeptide with a specified activity. The fact remains that the actual nucleic acid sequences which encode a protein with a particular activity or the actual amino acid sequences of such a protein *cannot* be envisioned any better when the possible choices are narrowed from all possible sequences, as essentially in claim 3, to all possible sequences with an arbitrary structural relationship with a known functional sequence, as in claims 1 or 2. For example, if one skilled in the art were to make a synthetic nucleotide sequence that encoded a polypeptide with 90% identity to the reference amino acid sequence, he

would be no more able to say whether it encoded a polypeptide with Cloaked-2 function than if the nucleotide sequence encoded a polypeptide that was only 10% identical to the reference polypeptide sequence - even were the Cloaked-2 function known. Nor would he be able to say whether the sequence existed in nature, as in the case of an allelic or splice variant.

The specification does not provide any information on what amino acid residues are necessary and sufficient for the undisclosed activity. The specification also provides no teachings on what amino acid sequence modifications, e.g. insertions, deletions and substitutions, would be permissible in a variant polypeptide that would improve or at least would not interfere with the biological activity or structural features necessary for the biological activity and stability of the protein. Since there were no other examples of a functional Cloaked-2 protein known that have structural homology with SEQ ID NO: 2 or 4, it is not possible to even guess at the amino acid residues which are critical to its structure or function based on sequence conservation. The comparison of SEQ ID NO: 2 to 4 is no help since it has not been disclosed whether these proteins share an activity, e.g. binding to a specific human receptor. Furthermore, it is known in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable (see Ngo, in The Protein Folding Problem and Tertiary Structure Prediction, Merz et al. (eds.), Birkhauser Boston: Boston, MA, pp. 433 and 492-495, 1994). Rudinger (in Peptide Hormones, Parsons (ed.), University Park Press: Baltimore, MD, pp. 1-7,

1976) discloses that even for peptide hormones, which are much smaller than the instant Cloaked-2 protein, one cannot predict variant amino acid sequences for a biologically active polypeptide. Rather one must engage in "case to case painstaking experimental study" to determine active variants (see page 7). Consequently, excessive trial and error experimentation would have been required to identify the necessary nucleic acid sequence derivatives encoding a protein with an activity of SEQ ID NO: 2 or 4 with an amino acid sequence differing from SEQ ID NO: 2 or 4 since the amino acid sequence of such polypeptides could not be predicted - even were the activity known.

As set forth in *In re Fisher,* 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

In *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991), the court ruled that a claim to a large genus of possible genetic sequences encoding a protein with a particular function that needs to be determined subsequent to the construction of the genetic sequences may not find sufficient support under 35 USC 112, 1st para., if only a few of the sequences that meet the functional limitations of the claim are disclosed and if undue

experimentation would be required of one skilled in the art for determining other genetic sequences embraced by the claim. This is the case here, where specification discloses only one putative functional amino acid sequences, SEQ ID NO: 2 or 4, for a polypeptide having the necessary activity, and provides no guidance on determining which polypeptide variants of SEQ ID NO: 2 or 4 which would have an activity of SEQ ID NO: 2 or 4.

To put the situation in perspective, the number of possible amino acid sequences of 190 amino acids in length is 20^{190} (approx. 10^{247}). The number of possible nucleotide or amino acid sequences that are of a given %identity relative to a reference sequence, where all differences between the possible sequences and the reference sequence are substitutions, can be calculated by the following expansion formula:

$$N = XL + X^2L(L-1)/2! + X^3L(L-1)(L-2)/3! + \ldots + X^{n-1}L(L-1)(L-2)\ldots(L-(n-2))/(n-1)! +$$

$$X^nL(L-1)(L-2)\ldots(L-(n-1))/n!$$

where N is the number of possible sequences, X is the number of different residues that can be substituted for a residue in the reference sequence, L is the length of the reference sequence, n is the maximum number of residues that can be substituted relative to the reference sequence at a given % identity. For a nucleotide sequence, X is 3 (alternate nucleotides); for an amino acid sequence, X is 19 (alternate amino acids). The n^{th} term of the expansion can be rewritten as:

$$X^n \cdot L!/(L-n)!n!$$

For a 190 amino acid sequence that is at least 90% identical to a reference sequence of 190 amino acids, e.g. SEQ ID NO: 2, the number of possible sequences having 18 amino acid substitutions relative to the reference (the penultimate term of the formula) is approximately 7×10^{47}, whereas the number of possible sequences having 19 amino acid substitutions relative to the reference (the final term of the formula) is approximately 1×10^{50}. So the last term is approximately equal to N, i.e. the preceding terms contribute little to the total. Also, as the number of permitted substitutions increases the number of possible variant sequences increases geometrically. In a genus of polypeptides that are at least 90% identical to a reference, nearly all will be exactly 90% identical. Claim 2 permits the polypeptide to share as little as 70% identity to SEQ ID NO: 2 or 4, which would include sequences with up to 57 amino acid substitutions. There would be approximately 10^{122} such sequences. While limiting the scope of potential sequences to those that are at least 70% or 90% identical to a reference greatly reduces the number of potential sequences to test, it does not do so in any meaningful way. The mass of the Earth is about 6×10^{24} kg. One microgram of 570 nucleotide dsDNA molecules (required to encode 190 amino acids) contains approximately 1.5×10^{12} DNA molecules. If it were possible to convert the mass of the Earth (6×10^{30} μg) into such DNA molecules, one would obtain about 10^{42} DNA molecules. Thus, one would require about 10,000,000 times the mass of the Earth of DNA to produce just one nucleic acid molecule encoding each of the 10^{50} possible amino acid sequences differing from SEQ ID NO: 2 or 4 by substitution of 10% of their amino acids.

Therefore, inclusion of the recited structural relationships in the claims do not distinguish the instant fact situation from those reviewed in *Amgen, Fiers,* and *Regents of the Univ. Calif.* Thus, even were an activity of human or murine Cloaked-2 disclosed, the instant specification would be inadequate to describe and enable how to make the nucleic acid molecules as broadly as they are claimed here.

Claims 1-5, 11, 52-54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "the encoded polypeptide" in part (c). Claim 2 recited "the polypeptide in line 2 of parts (c) and (e). There is insufficient antecedent basis for these limitations in the claims, as part (c) of claim 1 and parts (c) and (e) of claim 2 do not recite that the nucleotide sequence encodes a polypeptide.

Claim 2, parts (c) and (d), and claim 3, part (f), are ambiguous and improperly punctuated in the case of claim 2, parts (c) and (d). It is unclear what is intended here. It is unclear where "encoding a polypeptide fragment of at least 25 amino acids" and "comprising a fragment of at least about 16 nucleotides" fits in with the rest of the limitations. It is unclear what these fragments are fragments of.

Claim 11 is indefinite for recitation of "BLASTP, BLASTN, FASTA ...". These algorithms are improperly incorporated by reference into the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

Claims 1-5, 11, 52-54 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Brunkow et al. US 6,395,511, filed 11/24/99 claiming priority to 60/110,283 filed 11/27/98, which discloses the coding sequence for the human BEER polypeptide and the human BEER polypeptide and vectors, but does not disclose the murine sequences.

SEQ ID NO: 1 nucleotides 12-770 are identical to instant SEQ ID NO: 1, and encodes human BEER polypeptide, SEQ ID NO: 2, which is identical to instant SEQ ID NO: 5, and amino acids 24-213 of which are identical to instant SEQ ID NO: 2, i.e. it differs from instant SEQ ID NO: 2 insertion of 23 amino acids at the amino terminus. If the polypeptides of instant SEQ ID NO: 2 and 4 share an activity (which has not been disclosed in the instant specification), then the prior art polypeptide presumably has an activity of the polypeptide of instant SEQ ID NO: 4. Amino acids 24-213 differs from instant SEQ ID NO: 4 by 10 conservative substitutions, 8 non-conservative substitutions, and an insertion of 2 amino acids.

SEQ ID NO: 11, nucleotides 1-636 are identical to instant SEQ ID NO: 3, and encodes murine BEER polypeptide, SEQ ID NO: 12, which is identical to instant SEQ ID NO: 6, and where amino acids 24-211 are identical to instant SEQ ID NO: 4. If the polypeptides of instant SEQ ID NO: 2 and 4 share an activity (which has not been disclosed in the instant specification), then the prior art polypeptide presumably has an activity of the polypeptide of instant SEQ ID NO: 2. Amino acids 24-213 differs from instant SEQ ID NO: 2 by 10 conservative substitutions, 8 non-conservative substitutions, and an deletion of 2 amino acids.

Brunkow also discloses vectors containing these polynucleotides, including viral vectors, see col. 34-36.

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX numbers are (703) 308-4242 or (703) 305-3014 for any type of communication. In addition, FAX numbers for a computer server system using RightFAX are also available for communications before final rejection, (703) 872-9306, and for communications after final rejection, (703) 872-9307, which will generate a return receipt. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe whose telephone number is (703) 308-7310. The examiner can normally be reached on Monday through Friday from 8 AM to 4 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER